Increased incidence rate of hypothyroidism after iodine fortification in Denmark

A 20 year prospective population-based study

Petersen, Mads; Knudsen, Nils; Carlé, Allan; Andersen, Stig; Jørgensen, Torben; Perrild, Hans; Ovesen, Lars; Rasmussen, Lone Banke; Thuesen, Betina Heinsbæk; Pedersen, Inge Bülow

Published in:
Journal of Clinical Endocrinology and Metabolism

DOI (link to publication from Publisher):
10.1210/jc.2018-01993

Publication date:
2019

Document Version
Accepted author manuscript, peer reviewed version

Citation for published version (APA):
Petersen, M., Knudsen, N., Carlé, A., Andersen, S., Jørgensen, T., Perrild, H., Ovesen, L., Rasmussen, L. B., Thuesen, B. H., & Pedersen, I. B. (2019). Increased incidence rate of hypothyroidism after iodine fortification in Denmark: A 20 year prospective population-based study. *Journal of Clinical Endocrinology and Metabolism*, *104*(5), 1833–1840. [jc.2018-01993]. https://doi.org/10.1210/jc.2018-01993

ENDOCRINE SOCIETY

Increased incidence rate of hypothyroidism after iodine fortification in Denmark. A 20 year prospective population-based study.

Mads Petersen, Nils Knudsen, Allan Carlé, Stig Andersen, Torben Jørgensen, Hans Perrild, Lars Ovesen, Lone Banke Rasmussen, Betina Heinsbæk Thuesen, Inge Bülow Pedersen

The Journal of Clinical Endocrinology & Metabolism
Endocrine Society

Submitted: September 14, 2018
Accepted: December 11, 2018
First Online: December 14, 2018

The Journal of Clinical Endocrinology & Metabolism; Copyright 2018 DOI: 10.1210/jc.2018-01993

Incidence of hypothyroidism after iodine fortification in Denmark

Increased incidence rate of hypothyroidism after iodine fortification in Denmark. A 20 year prospective population-based study.

Mads Petersen[1], Nils Knudsen[2], Allan Carlé[1], Stig Andersen[3], Torben Jørgensen[4,5,6], Hans Perrild[2], Lars Ovesen[7], Lone Banke Rasmussen[2], Betina Heinsbæk Thuesen[4], Inge Bülow Pedersen[1]

[1]Department of Endocrinology, Aalborg University Hospital, Denmark. [2]Department of Endocrinology, Bispebjerg Hospital, University of Copenhagen, Denmark. [3]Department of Geriatrics, Aalborg University Hospital, Denmark. [4]Centre for Clinical Research and Prevention, Bispebjerg/Frederiksberg Hospital, Denmark. [5]Department of Public Health, Faculty of Health Sciences, University of Copenhagen. [6]Faculty of Medicine, Aalborg University. [7]Department of Gastroenterology, Slagelse Hospital.

ORCiD numbers:

0000-0002-1238-7850

Petersen

Mads

Received 14 September 2018. Accepted 11 December 2018.

Objective: To monitor the impact of a cautious iodine fortification (IF) on the incidence of overt hypothyroidism in two sub-populations with different levels of preexisting iodine deficiency (ID).
Design: A 20 years (1997-2016) prospective population-based study identified all new cases of diagnosed overt biochemical hypothyroidism in two open cohorts: a Western cohort with moderate ID (n=309,434, January 1st, 1997) and an Eastern cohort with mild ID (n=224,535, January 1st, 1997). A diagnostic algorithm was applied to all thyroid function tests performed within the study areas and possible new cases were verified individually. Mandatory IF of salt was initiated in mid-2000 (13 p.p.m.). The present study is a part of the DanThyr study.
Results: At baseline, standardized incidence rate (SIR) of hypothyroidism was 32.9 and 47.3/100.000/year in the cohort with moderate and mild ID, respectively. The SIR of hypothyroidism increased significantly in both cohorts after implementing mandatory IF with peak values of 150 % in 2014-16 for the moderate ID cohort and 130 % in 2004-05 for the mild ID cohort. Significant increases in SIR were seen among the young and middle aged of both cohorts, whereas no changes were seen among the elderly (60+ y). The follow-up period for the mildly iodine deficient cohort was restricted up to and including 2008.
Conclusion: The cautious initiation of the IF program in Denmark caused a sustained increase in hypothyroidism incidence among subjects residing areas of moderate and mild iodine deficiency, but only among the young and middle aged.

The incidence rate of hypothyroidism has increased in Denmark after the introduction of iodine fortification of salt. Results from a 20 year prospective population-based study.

Introduction

Iodine deficiency (ID) is one of the most common types of specific nutritional deficiencies globally. Endemic goiter is common in severe ID areas and endemic cretinism with mental retardation may also result from severe ID[1]. Moderate and mild ID is associated with a high prevalence of toxic and nontoxic multinodular goitre[1,2].

According to the World Health Organization (WHO) recommendations, the daily iodine intake for men, non-pregnant women and children above 12 years of age should be around 150 µg[1]. Worldwide iodine fortification (IF) programs cover around two thirds of the world's population[1], which have eradicated or reduced the risk of ID disorders in many countries.

It is well known that increasing the daily iodine intake in a population with mild and moderate ID causes a transient increase in incidence of hyperthyroidism know as iodine induced hyperthyroidism (IIH)[3]. Furthermore, some have reported increased occurrence of hypothyroidism following IF[4–6]. Still, little is known about the magnitude and possible reversibility of this increase in hypothyroidism. Also, the role of the pre-fortification level of ID in relation to a specific increase in iodine intake remains to be elucidated.

Prior to 1998 Denmark was a country of iodine deficiency. Mild ID dominated in the Eastern part of Denmark and moderate ID in the Western part[7]. The low iodine intake was associated with both toxic and non-toxic multinodular goiter especially among the elderly, and insufficient thyroid hormone production in pregnant women was suggested by an increase in s-TSH in late pregnancy[8–10]. Consequently, voluntary IF of salt was cautiously (8 p.p.m.) initiated in July 1998[11]. The IF program aimed to increase the average daily iodine intake by 50 µg/day. However, this turned out to be ineffective and from July 2000 the iodization of bread and household salt was made mandatory at the level of 13 p.p.m.[11,12]. An iodine monitoring program: "The Danish Investigation of Iodine Intake and Thyroid Disorders" (DanThyr) was established to monitor the implementation of salt iodization in Denmark[7].

The influence of IF on the incidence rate of hypothyroidism in Denmark has been described for the early years of IF[4]. In the present study we performed a long-term follow-up on the incidence of hypothyroidism in two areas of Denmark with previous mild ID and moderate ID. The follow-up time for the area with moderate ID was 17 years past mandatory IF thus ending in December 2016, while staff limitations caused a shorter follow-up of 9 years in the area with mild ID which ended in October 2008. The present study is part of the DanThyr study.

Methods and Materials

Population cohort

Two open cohorts were selected, one with moderate ID prior to IF (Aalborg city and the surrounding municipalities, n=309,434 by January 1st, 1997; median urinary iodine concentration (UIC): 45 µg/l in subjects not using iodine containing supplements; 53 µg/l if all subjects were included)[13], and one with only mild ID (located in the Danish capital Copenhagen, n=224,535 by January 1st, 1997; median UIC: 61 µg/l in subjects not taking iodine containing supplements; 68 µg/l if all subjects were included)[13]. Detailed information on the composition of these two cohorts was provided yearly by Statistics Denmark[14]. As part of a national structural reform, the boundaries of the Danish municipalities were restructured in January 2007. Therefore, the cohort size became smaller in the moderate ID area (n=261,569 by January 1st, 2007), but remained unaltered in the mild ID cohort.

The iodine status in the study areas changed during the study period. As part of the DanThyr study two cross-sectional studies and a follow-up study were performed in the two cohort areas in parallel with the present study. The 1st cross-sectional study took place at baseline (1997-98) before IF and the 2nd study in 2004-05 while a follow-up study to the initial cross-sectional study was conducted in 2008-10. Median UIC in the Western and Eastern cohort were determined at each study respectively (1st: 45 vs 61 µg/l, 2nd: 86 vs 99 µg/l[15], follow-up: 73 vs 76 µg/l[16]). Thus, a small decrease in iodine intake level was observed during late mandatory IF. This decrease was likely caused by a diminished iodine intake from dairy products[17].

Identification of new cases of hypothyroidism

The register database used in the present study and the evaluation of the database have been described in detail previously [13]. A brief summary:

In the Western cohort with moderate ID a single laboratory at Aalborg University Hospital handled all thyroid function tests, whereas three laboratories covered the Eastern cohort with mild ID (the laboratories at Frederiksberg and Bispebjerg Hospitals and the General Practitioners Laboratory in Copenhagen).

All general practitioners, hospital departments and private practice specialists in Denmark have unique referral identification numbers utilized for laboratory services. All Danish citizens have a unique identification number in the Centralized Person Register (CPR). The CPR numbers and the unique referral identification numbers made it possible to identify potential new cases of hypothyroidism within the selected area by monitoring results of thyroid function tests as follows: All laboratory tests for serum thyroid stimulating hormone (TSH) and estimates of thyroxine (T_4) sampled within the cohort areas were recorded in a specially designed register database[13] (*figure 1)*. Potential new cases of overt hypothyroidism were identified by an elevated serum TSH (>5.0mU/l) combined with a low serum T_4 estimate. Specific reference ranges were utilized for the evaluation of low T_4 according to the standards of each laboratory as described previously[13]. Cases previously recorded and verified in the database as either hyper- or hypothyroid were marked as "known". Each potential new case was then scrutinized individually by contacting the requesting physician or through available hospital records. Hence, we identified and verified all new cases of diagnosed hypothyroidism among individuals tested within the cohort areas.

Statistical methods

We adjusted for changes in sex and age composition of the cohort and calculated the standardized incidence rate (SIR) using the method of direct standardization[18]. The Danish population at January 1st 2005 was used as the standard population[14]. Significance to baseline SIR was calculated using the 95% confidence intervals (95% CI) of the standardized incidence rate ratio (SIRR)[18].The SIR is given in cases per 100,000 person years. For the statistical analysis we used IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.

The present study was approved by the National Committee on Health Research Ethics in Denmark and by The Danish Data Protection Agency.

Results

Overall incidence rates of diagnosed hypothyroidism

The baseline SIR of hypothyroidism in the Western cohort with moderate ID was 32.9 compared to 47.3 per 100,000-person years in the Eastern cohort with mild ID (SIRR: 0.69; 95% CI: 0.54-0.90). No significant increase in incidence rate of hypothyroidism was seen in either of the two cohorts during the initial voluntary IF (mid1998-mid2000). The SIR of hypothyroidism increased significantly in both cohorts following mandatory IF *(figure 2)*. In the Western cohort with previous moderate ID the incidence rate of hypothyroidism increased further during the extended study period and peaked in the last three years of the study (2014-16) with a SIRR to baseline: 1.50 (95% CI: 1.25-1.81). In the Eastern cohort the increase in incidence rate came later and was significant from 2004-05 (SIRR to baseline was: 1.30 (95% CI: 1.06-1.60)) and until 2007 only. The SIR of hypothyroidism reached a maximum in 2008, though this was not statistically significantly different from the baseline level.

For each time period the incidence rate of hypothyroidism was higher in the cohort with mild compared to moderate ID (*figure 2*).

Gender specific incidence rates of hypothyroidism

In females the SIR of hypothyroidism prior to IF was 53.8 and 72.2 /100.000/y in the area of moderate and mild ID respectively. SIR increased in females in the mild ID cohort and reached statistical significance by the years 2002-03 and seems to have reached a plateau. Thus, SIRR to baseline was 1.29 (95% CI: 1.02-1.62) in 2004-05, and in 2006-07 SIRR to baseline: 1.27 (95% CI: 1.01-1.61) (*figure 3*). Interestingly, the increase in SIR among females in the moderate ID cohort was not statistically significantly until the very last years of the study period (year 2014-16, SIRR: 1.31; 95% CI: 1.06-1.63) (*figure 3*).

In males the SIR of hypothyroidism at baseline was 11.4 vs. 21.8 /100.000/y (moderate vs. mild ID). The incidence rate of hypothyroidism increased after initiation of mandatory IF in the cohort with moderate ID *(figure 3)*. The rise was statistically significant from the years 2001-02 and onward. Peak value was reached in 2012-13 with a SIRR of 2.54 (95% CI: 1.66-3.90) *(figure 3)*. The incidence rate seen in men in the mild ID cohort did not change significantly.

Age specific incidence rates of hypothyroidism

The incidence rates of hypothyroidism were highly correlated with age in both cohorts throughout the study period.

In the Western cohort with previously moderate ID, the baseline SIRs of the young (20-39 years), middle-aged (40-59 years) and elderly (60+ years) were 14.5, 30.8 and 92.2 /100.000/y respectively *(figure 4a)*. The incidence rate of hypothyroidism in the young rose continuously until 2012-13 where it levelled off at a SIRR of 2.80 (95% CI: 1.67-4.70) compared to baseline. The middle-aged from this cohort also experienced an early increase in SIR of hypothyroidism reaching a peak value by 2014-16 with a SIRR of 2.16 (95% CI: 1.55-3.01) compared to baseline *(figure 4a)*. The changes in the elderly were limited and non-significant throughout the study period.

In the Eastern cohort with previous mild ID the baseline SIR of the young (20-39 y), middle-aged (40-59 y) and elderly (60+ y) were 16.4, 42.2 and 148.3 /100.000/y respectively *(figure 4b)*. Following mandatory IF SIR rose in both the young and the middle-aged. It peaked in the younger age group by 2008 with a SIRR of 2.62 (95% CI: 1.36-5.04) compared to baseline. The elevation in SIR among the middle-aged was present from 2004-07 with peak value in 2006-07 (SIRR compared to baseline: 2.19; 95% CI: 1.49-3.23). The SIR decreased by the end of the study period for the middle-aged. The fluctuations seen in the elderly (60+y) during the study period showed no systematic change in incidence following IF.

Discussion

Principal observations

Implementation of IF in Denmark was followed by a marked rise in the overall incidence rate of diagnosed hypothyroidism. Peak incidence rates were reached by 2012-2016 in moderate ID and by 2004-2008 in mild ID. Significant increases in incidence rates of hypothyroidism were seen in the women from both cohorts after introduction of mandatory IF, whereas only men from the moderate ID cohort responded to IF with an increased incidence rate. The increase in incidence rate of hypothyroidism was highly age-dependent and observed only in the young and middle aged from both cohorts. The incidence rate of hypothyroidism decreased by 2008 to a level not statistically significantly different from baseline level in the middle-aged women in the mild ID cohort.

Comparison with other studies

A high occurrence of hypothyroidism has been widely reported in populations with a high stable iodine intake[19–22]. Szabolcs et al.[19] investigated the prevalence of overt and subclinical hypothyroidism in three areas in Slovakia and Hungary with different urinary iodine levels (median UIC 72, 100 and 513µg/g creatinine respectively) and found prevalences of overt hypothyroidism of 0.8, 1.5, and 7.6% respectively (prevalences of subclinical hypothyroidism: 4.2, 10.4, and 23.9%).

A large cross-sectional study dealing with the correlation between iodine intake and the prevalence of thyroid disorders was published in 2016 by Shan et al.[20]. Iodine excretion and thyroid disease frequency was surveyed in 15,008 subjects from 10 different Chinese cities after a 16 year period of varying mandatory salt iodization with an initial excessive iodine intake that was adjusted several times over the years to approach adequate iodine intake. Six cities were categorized as having adequate iodine intake (median UIC between 100 and 200 µg/l) and four cities had more than adequate iodine intake (median UIC between 200 and 300 µg/l). A higher prevalence of both overt and subclinical hypothyroidism was reported in the cities with more than adequate iodine intake compared to those with just adequate intake (prevalence rate: overt hypothyroidism (1.3 vs 1.0%) and subclinical hypothyroidism (22.6 vs 12.7%)).

Jeon et al. [21] investigated 6,564 participants of both genders and all age groups. The overall median UIC was 299.3 µg/l with an interquartile range of 158.8-699.8 µg/l. The subjects were divided into six groups based on their UIC, ranging from moderately/severe ID to extremely excessive iodine excretion. In the iodine-excessive groups the s-TSH levels were right-shifted when compared to those in the adequate iodine intake group while the TSH levels were left-shifted in the iodine-deficient groups. This supports the correlation between the frequency of thyroid failure and iodine intake over a wide range[21].

The results of the present study are in accordance with the positive association found between the frequency of thyroid failure and the magnitude of iodine intake among different populations[19–22]. Prior to IF, we found a 44% higher incidence rate of hypothyroidism in the Eastern cohort with mild ID compared to the Western cohort with moderate ID. It seems thus that very small differences in iodine intake influences the occurrence of hypothyroidism even within the ID range[23].

An increase in the occurrence of hypothyroidism has also been reported from other areas undergoing iodine fortification[22,24,25]. The Pescopagano survey of voluntary IF of salt in Italy described a markedly higher prevalence of clinical and subclinical hypothyroidism in the study population after 15 years (2.8% in 1995 vs 5.0% in 2010)[25]. This was mainly due to an increased frequency of subclinical hypothyroidism in children (<15 y). In addition, they reported an increased prevalence of thyroid autoantibodies by the year 2010 compared to 1995 (19.5% vs 12.6%)[25].

An increase in median TSH (1.30 to 1.51 mU/l) was reported from the first cross-sectional study within the cohort areas at baseline (1997-98) to the second cross-sectional study after implementation of mandatory IF (2004-05)[26]. This increase was in part caused by fewer cases of suppressed TSH, but also due to an increase in autoimmune thyroid failure, as suggested by the increased presence of thyroid autoantibodies (TPO-Ab and/or Tg-Ab)[27]. An increase in the prevalence of thyroid autoantibodies in the population was evident from the first to the second cross-sectional study (TPO-Ab: 14.3 vs. 23.8 % and Tg-Ab: 13.7 vs. 19.9 %)[27]. Interestingly, this increase was most pronounced in young adults who also had the highest increase in the incidence of hypothyroidism in the present study.

Monitoring the use of thyroid medication on a nationwide scale in Denmark before and after IF showed a marked increase in the use of thyroid hormone replacement therapy in areas with previously moderate and mild ID alike.[28] This is in keeping with our findings of increased occurrence of thyroid failure in both cohort areas.

Prior to IF in Denmark, 50% of patients diagnosed with spontaneous autoimmune thyroid failure were 68 years or above in the two cohort areas of the present study[29]. We found an increase in the incidence of hypothyroidism among only the young and middle-aged. Evidently the mechanism responsible for increasing the incidence rate of hypothyroidism after introduction of IF does not significantly affect the elderly.

It seems possible that the slight decrease in incidence rate of hypothyroidism observed in our cohort with previous moderate ID during the years 2008-11 could be explained by a likely decrease in median UIC found during this period (from 86 µg/l in 2004 to 73 in 2008)[17]. Likewise, it could be speculated that the iodine intake in the Western cohort may have risen during the following years thus explaining the observed increase in incidence rate toward the end of the study (2012-16). One could notice that the incidence rate within the Western cohort in the final years (2014-16) is remarkably similar to the incidence rate observed in the Eastern cohort at baseline value prior to any IF. It would seem likely that these similar incidence rates of hypothyroidism could result from equal median UIC between these two areas at the time periods specified. Though newer studies of iodine excretion in the Western cohort are needed to confirm this.

Possible mechanisms involved

From the cross-sectional studies performed in parallel with our current cohort study as part of the DanThyr study complex, we have solid evidence that the prevalence of TPO antibody positivity increased significantly 4-5 years after the implementation of mandatory iodine fortification[27]. Interestingly, the increase in prevalence of TPO-Ab positivity was most pronounced among the younger age groups and least among the elderly[27]. Results from the same cross-sectional study clearly indicate a distinct association between elevated TSH and TPO-Ab level[27,30]. This is in accordance with the findings of the present study as the younger age group experienced the greatest increase in incidence rate of hypothyroidism, which is as expected given the substantial increase in the TPO-Ab prevalence of this age group. These results heavily suggests that thyroid autoimmunity was a main cause of the rise in hypothyroidism incidence found in the present study[27]. This is in keeping with other studies suggesting autoimmunity as a possible explanation for the increased occurrence of hypothyroidism after initiation of IF[5,31–33]. In addition, auto-regulatory processes within the thyroid gland, possibly involving the production of iodine containing derivates of arachidonic acid in response to increased iodine intake as a mean to protect against an iodine overload, may also be involved in inducing hypothyroidism[34].

Denmark has seen an increased focus on thyroid dysfunction over the course of our study period. An increased diagnostic activity could result and lead to more hypothyroid patients being identified as the study progressed. Indeed significant reductions in the prevalence of undiagnosed overt hypothyroidism was observed in both study areas in the cross-sectional cohorts after the initiation of IF[26]. In the present study we found substantial increase in the incidence of TSH measurements performed within both areas during the course of the study. However, we cannot easily separate diagnostic activity from increased monitoring of patients with known thyroid disease.

The impact of IF on the distribution of the nosological subtypes of hypothyroidism remains to be elucidated and may contribute to explaining the mechanisms responsible for at least part of the increase in hypothyroid cases seen in this study.

Implications for IF programs

A small increase in the daily iodine intake of 50 µg or less caused an increase of 30 and 50% in the incidence rate of hypothyroidism in subjects with mild and moderate ID respectively. It seems that IF even at this low level induces increased hypothyroidism in moderately and in mildly iodine deficient populations. Thus, a cautious approach to IF in an iodine deficient population should be recommended. Specific attention may be given to the young and middle-aged subjects when implementing IF, as the overall increase in incidence of hypothyroidism seemed to exclusively affect these age groups while the incidence rate of hypothyroidism among the elderly seemed completely unaffected in both cohorts.

Strengths and limitations

Our inclusion of all thyroid function tests among general practitioners, specialists with private practice and hospital departments reduced the referral biases frequently associated with studying the development in incidence rates of thyroid disease before and after IF [35]. Present study thus ensures the inclusion of subjects with all degrees of overt biochemical hypothyroidism.

Our methods do not provide information about the duration or severity of the biochemically hypothyroid cases identified in the two cohorts. It may be speculated that some of the increase in incidence rate of diagnosed hypothyroidism relates to mild or transitory cases of hypothyroidism. This is an important topic for future studies.

The relatively low frequency of hypothyroidism in areas with iodine deficiency necessitated the inclusion of a substantial number of subjects in the cohorts in order to gain the statistical power for analysis. As such, not all subjects within the cohorts underwent thyroid function measurements each year given the insurmountable resources required for such a task. The incidence rates described in the current study specifically refers to the incidence of diagnosed hypothyroidism and thus does not include potential cases of hypothyroidism where no thyroid function tests have been performed.

Treatment of subclinical hypothyroidism may have occurred more frequently as the study progressed. This would lead to an underestimation of the true level of hypothyroidism caused by IF, as initiation of thyroid hormone substitution in subjects with subclinical hypothyroidism may cause their thyroid hormone levels to remain within the reference range and thus never become overtly hypothyroid.

Conclusion

Mandatory iodine fortification increased the incidence rate of hypothyroidism in both mildly and moderately iodine deficient parts of Denmark in less than four years. This elevated level was upheld by 17 years following mandatory IF. Further studies are needed for clarifying the subtypes, severity and duration of hypothyroidism after the introduction of IF.

The Danish Medical Foundation, Not Applicable; BRAHMS Diagnostica, Not Applicable; The Health Insurance Foundation, Not Applicable; The 1991 Pharmacy Foundation, Not Applicable; The Copenhagen Hospital Corporation Research Foundation, Not Applicable; North Jutland County Research Foundation, Not Applicable; Tømmerhandler Vilhelm Bang Foundation, Not Applicable

Correspondence: Mads Petersen, MD, Department of Endocrinology, Aalborg University Hospital, Sdr. Skovvej 15, 9000 Aalborg, Tel. 004522447966, E-mail: mads.petersen@rn.dk

Disclosure statement:
the authors have nothing to disclose

References

1. Assessment of iodine deficiency disorders and monitoring their elimination A GUIDE FOR PROGRAMME MANAGERS Third edition. https://www.unicef.org/ukraine/2_Guide_for_IDD_managers_eng.pdf. Accessed October 6, 2017.

2. Carlé A, Pedersen IB, Knudsen N, et al. Epidemiology of subtypes of hyperthyroidism in Denmark: a population-based study. *Eur J Endocrinol*. 2011;164(5):801-809. doi:10.1530/EJE-10-1155.
3. Stanbury JB, Ermans AE, Bourdoux P, et al. Iodine-induced hyperthyroidism: occurrence and epidemiology. *Thyroid*. 1998;8(1):83-100.
4. Pedersen IB, Laurberg P, Knudsen N, et al. An increased incidence of overt hypothyroidism after iodine fortification of salt in Denmark: a prospective population study. *J Clin Endocrinol Metab*. 2007;92(8):3122-3127. doi:10.1210/jc.2007-0732.
5. Delange F. The disorders induced by iodine deficiency. *Thyroid*. 1994;4(1):107-128. doi:10.1089/thy.1994.4.107.
6. Sun X, Shan Z, Teng W. Effects of increased iodine intake on thyroid disorders. *Endocrinol Metab (Seoul, Korea)*. 2014;29(3):240-247. doi:10.3803/EnM.2014.29.3.240.
7. Laurberg P, Jørgensen T, Perrild H, et al. The Danish investigation on iodine intake and thyroid disease, DanThyr: status and perspectives. *Eur J Endocrinol*. 2006;155(2):219-228. doi:10.1530/eje.1.02210.
8. Pedersen KM, Borlum KG, Knudsen PR, Hansen E-S, Johannesen PL, Laurberg P. Urinary iodine excretion is low and serum thyroglobulin high in pregnant women in parts of Denmark. *Acta Obstet Gynecol Scand*. 1988;67(5):413-416. doi:10.3109/00016348809004251.
9. Pedersen KM, Laurberg P, Iversen E, et al. Amelioration of some pregnancy-associated variations in thyroid function by iodine supplementation. *J Clin Endocrinol Metab*. 1993;77(4):1078-1083. doi:10.1210/jcem.77.4.8408456.
10. Nøhr SB, Laurberg P, Børlum K-G, et al. Iodine deficiency in pregnancy in Denmark: Regional variations and frequency of individual iodine supplementation. *Acta Obstet Gynecol Scand*. 1993;72(5):350-353. doi:10.3109/00016349309021111.
11. Rasmussen LB, Andersson G, Haraldsdóttir J, et al. Iodine. Do we need an enrichment program in Denmark? *Int J Food Sci Nutr*. 1996;47(5):377-381. http://www.ncbi.nlm.nih.gov/pubmed/8889622.
12. Jensen HG, Strube M. *Bekendtgørelse Om Tilsætning Af Jod Til Husholdningssalt Og Salt I Brød Og Almindeligt Bagværk M.v.*; 1998.
13. Pedersen IB, Laurberg P, Arnfred T, et al. Surveillance of disease frequency in a population by linkage to diagnostic laboratory databases. A system for monitoring the incidences of hyper- and hypothyroidism as part of the Danish iodine supplementation program. *Comput Methods Programs Biomed*. 2002;67(3):209-216. http://www.ncbi.nlm.nih.gov/pubmed/11853947.
14. Statistics Denmark. Available on http://www.dst.dk.
15. Vejbjerg P, Knudsen N, Perrild H, et al. Effect of a mandatory iodization program on thyroid gland volume based on individuals' age, gender, and preceding severity of dietary iodine deficiency: a prospective, population-based study. *J Clin Endocrinol Metab*. 2007;92(4):1397-1401. doi:10.1210/jc.2006-2580.
16. Rasmussen LB, Jørgensen T, Perrild H, et al. Mandatory iodine fortification of bread and salt increases iodine excretion in adults in Denmark - a 11-year follow-up study. *Clin Nutr*. 2014;33(6):1033-1040. doi:10.1016/j.clnu.2013.10.024.
17. Rasmussen LB, Krejbjerg A, Jørgen J, et al. Iodine excretion has decreased in Denmark between 2004 and 2010 -the importance of iodine content in milk – the importance of iodine content in milk. *Br J Nutr*. 2016;112(12). doi:10.1017/s0007114514003225.
18. Boyle P, Parkin DM. Chapter 11. Statistical methods for registries. https://www.iarc.fr/en/publications/pdfs-online/epi/sp95/sp95-chap11.pdf. Accessed November 20, 2017.

19. Szabolcs I, Podoba J, Feldkamp J, et al. Comparative screening for thyroid disorders in old age in areas of iodine deficiency, long-term iodine prophylaxis and abundant iodine intake. *Clin Endocrinol (Oxf)*. 1997;47(1):87-92. http://www.ncbi.nlm.nih.gov/pubmed/9302377.
20. Shan Z, Chen L, Lian X, et al. Iodine status and prevalence of thyroid disorders after introduction of mandatory universal salt iodization for 16 years in China: a cross-sectional study in 10 cities. *Thyroid*. 2016;26(8):1125-1130. doi:10.1089/thy.2015.0613.
21. Jeon MJ, Kim WG, Kwon H, et al. Excessive iodine intake and thyrotropin reference interval: data from the korean national health and nutrition examination survey. *Thyroid*. 2017;27(7):967-972. doi:10.1089/thy.2017.0078.
22. Laurberg P, Pedersen KM, Hreidarsson A, Sigfusson N, Iversen E, Knudsen PR. Iodine intake and the pattern of thyroid disorders: a comparative epidemiological study of thyroid abnormalities in the elderly in Iceland and in Jutland, Denmark. *J Clin Endocrinol Metab*. 1998;83(3):765-769. doi:10.1210/jcem.83.3.4624.
23. Petersen M, Knudsen N, Carlé A, et al. Thyrotoxicosis after iodine fortification. A 21-year Danish population-based study. *Clin Endocrinol (Oxf)*. June 2018. doi:10.1111/cen.13751.
24. Teng W, Shan Z, Teng X, et al. Effect of iodine intake on thyroid diseases in China. *N Engl J Med*. 2006;354(26):2783-2793. doi:10.1056/NEJMoa054022.
25. Aghini Lombardi F, Fiore E, Tonacchera M, et al. The effect of voluntary iodine prophylaxis in a small rural community: The Pescopagano Survey 15 years later. *J Clin Endocrinol Metab*. 2013;98(3):1031-1039. doi:10.1210/jc.2012-2960.
26. Vejbjerg P, Knudsen N, Perrild H, et al. Lower prevalence of mild hyperthyroidism related to a higher iodine intake in the population: prospective study of a mandatory iodization programme. *Clin Endocrinol (Oxf)*. 2009;71(3):440-445. doi:10.1111/j.1365-2265.2008.03493.x.
27. Pedersen IB, Knudsen N, Carlé A, et al. A cautious iodization programme bringing iodine intake to a low recommended level is associated with an increase in the prevalence of thyroid autoantibodies in the population. *Clin Endocrinol (Oxf)*. 2011;75(1):120-126. doi:10.1111/j.1365-2265.2011.04008.x.
28. Møllehave LT, Linneberg A, Skaaby T, Knudsen N, Jørgensen T, Thuesen BH. Trends in treatments of thyroid disease following iodine fortification in Denmark: a nationwide register-based study. *Clin Epidemiol*. 2018;10:763-770. doi:10.2147/CLEP.S164824.
29. Carlé A, Laurberg P, Pedersen IB, et al. Epidemiology of subtypes of hypothyroidism in Denmark. *Eur J Endocrinol*. 2006;154(1):21-28. doi:10.1530/eje.1.02068.
30. Pedersen IB, Laurberg P, Knudsen N, et al. A population study of the association between thyroid autoantibodies in serum and abnormalities in thyroid function and structure. *Clin Endocrinol (Oxf)*. 2005;62(6):713-720. doi:10.1111/j.1365-2265.2005.02284.x.
31. Ferrari SM, Fallahi P, Antonelli A, Benvenga S. Environmental issues in thyroid diseases. *Front Endocrinol (Lausanne)*. 2017;8:50. doi:10.3389/fendo.2017.00050.
32. Hu S, Rayman MP. Multiple nutritional factors and the risk of Hashimoto's Thyroiditis. *Thyroid*. 2017;27(5):597-610. doi:10.1089/thy.2016.0635.
33. Latrofa F, Fiore E, Rago T, et al. Iodine contributes to thyroid autoimmunity in humans by unmasking a cryptic epitope on thyroglobulin. *J Clin Endocrinol Metab*. 2013;98(11):E1768-E1774. doi:10.1210/jc.2013-2912.
34. Chazenbalk GD, Valsecchi RM, Krawiec L, et al. Thyroid autoregulation. Inhibitory effects of iodinated derivatives of arachidonic acid on iodine metabolism. *Prostaglandins*. 1988;36(2):163-172. http://www.ncbi.nlm.nih.gov/pubmed/3141976.

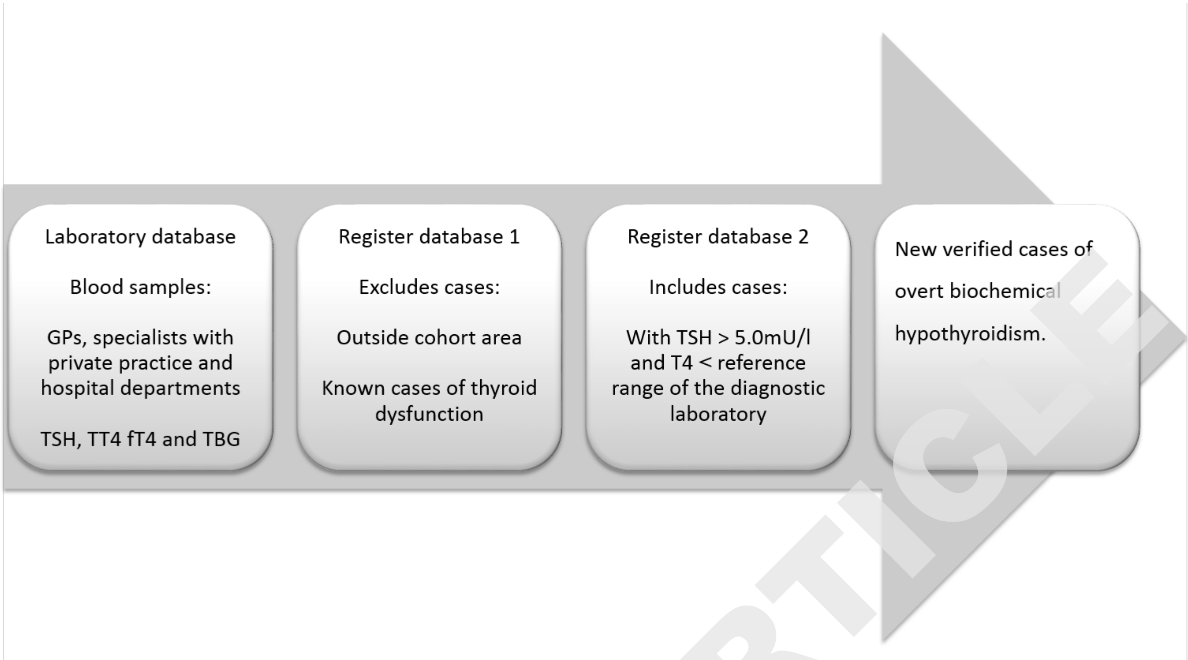
35. Carlé A, Pedersen IB, Perrild H, Ovesen L, Jørgensen T, Laurberg P. High age predicts low referral of hyperthyroid patients to specialized hospital departments: evidence for referral bias. *Thyroid.* 2013;23(12):1518-1524. doi:10.1089/thy.2013.0074.

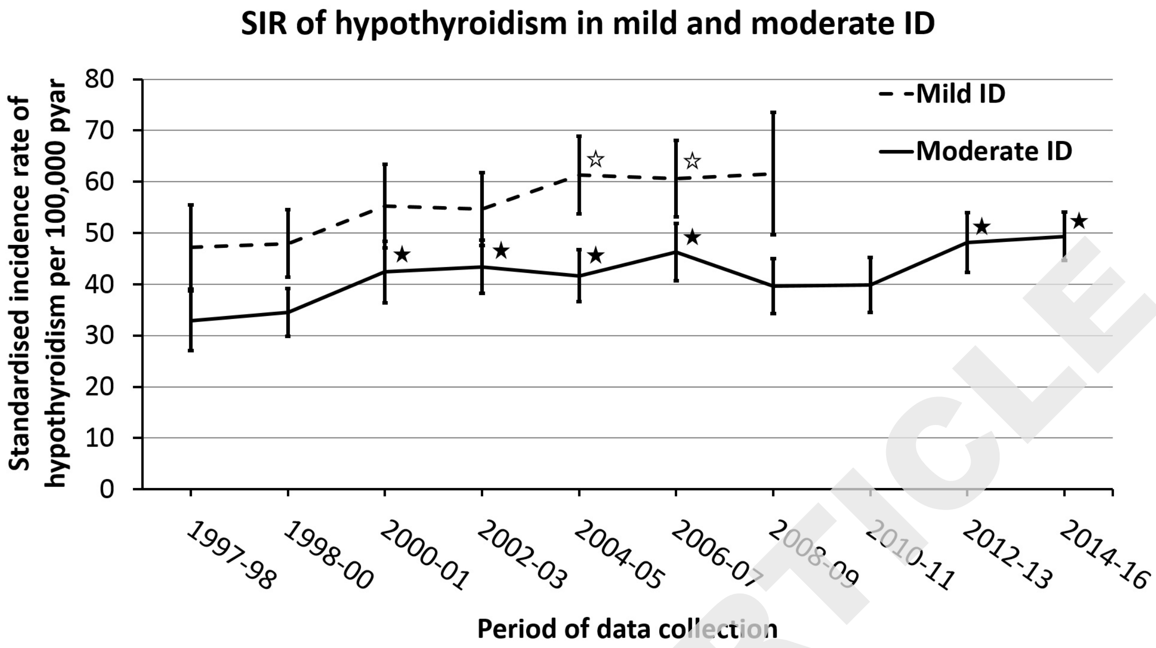
Figure 1: Flowchart showing how new cases of overt biochemical hypothyroidism were identified in both cohorts. Subjects on the list of possible new cases were individually verified through contact to the physician who requested the initial blood test and through available hospital records.

Figure 2: The standardized incidence rates of hypothyroidism per 100,000 person year (pyar) in the cohorts with mild (dotted) and moderate (solid) ID. The rates are sex and age standardized to the Danish population of the year 2005. The error bars indicate the 95 % confidence intervals (CI) for the incidence rates. Voluntary IF: initiated in July 1998 with 8 ppm iodine in table salt and salt used by the food industry. Mandatory IF: initiated in July 2000 with 13 ppm iodine in all table salt and salt used for the production of bread. Stars indicate statistical significance to baseline. Moderate ID: Mild ID: The study period for the mildly iodine deficient cohort was concluded by the end of September 2008.

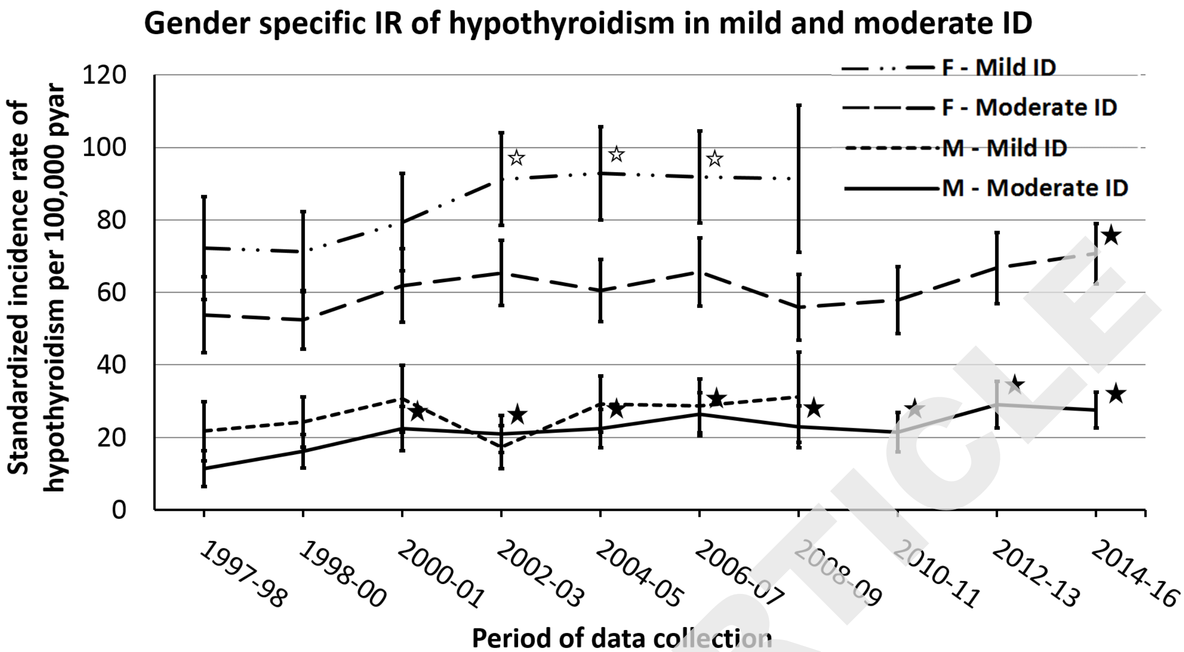
Figure 3: Gender specific incidence rates with 95% CI of hypothyroidism per 100,000 person year (pyar) among men (M) and women (F) for both cohorts. Stars indicate statistical significance to baseline. Moderate ID: ★Mild ID: ✰Incidence rates were standardized for age.

Figure 4 a-b: Age specific incidence rates of hypothyroidism per 100,000 person year (pyar) with 95% CI in the following age groups: 20-39, 40-59 and 60+ years for the area of moderate ID (a) and mild ID (b). Stars indicate statistical significance to baseline. Moderate ID: ★ Mild ID: ✰Incidence rates were standardized for age and gender.

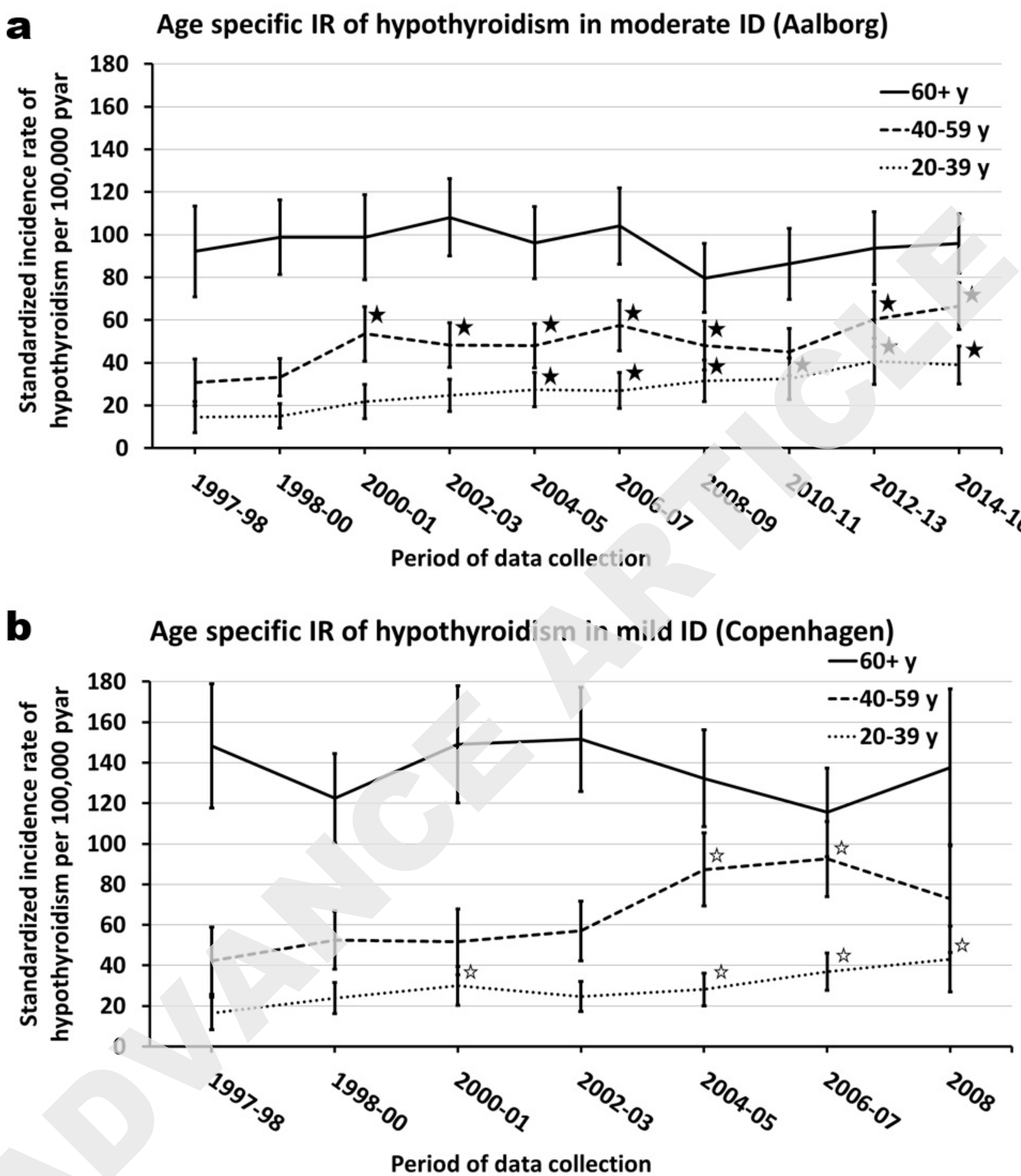

Laboratory database
Blood samples:
GPs, specialists with private practice and hospital departments
TSH, TT4 fT4 and TBG
Register database 1
Excludes cases:
Outside cohort area
Known cases of thyroid dysfunction
Register database 2
Includes cases:
With TSH > 5.0mU/l and T4 < reference range of the diagnostic laboratory
New verified cases of overt biochemical hypothyroidism.



SIR of hypothyroidism in mild and moderate ID
Standardised incidence rate of hypothyroidism per 100,000 pyar
80
70
60
50
40
30
20
10
0
Mild ID
Moderate ID
1997-98
1998-00
2000-01
2002-03
2004-05
2006-07
2008-09
2010-11
2012-13
2014-16
Period of data collection



Gender specific IR of hypothyroidism in mild and moderate ID
Standardized incidence rate of hypothyroidism per 100,000 pyar
120
100
80
60
40
20
0
F - Mild ID
F - Moderate ID
M - Mild ID
M - Moderate ID
1997-98
1998-00
2000-01
2002-03
2004-05
2006-07
2008-09
2010-11
2012-13
2014-16
Period of data collection


a
Age specific IR of hypothyroidism in moderate ID (Aalborg)
Standardized incidence rate of hypothyroidism per 100,000 pyar
60+ y
40-59 y
20-39 y
Period of data collection
1997-98
1998-00
2000-01
2002-03
2004-05
2006-07
2008-09
2010-11
2012-13
2014-16
b
Age specific IR of hypothyroidism in mild ID (Copenhagen)
Standardized incidence rate of hypothyroidism per 100,000 pyar
60+ y
40-59 y
20-39 y
Period of data collection
1997-98
1998-00
2000-01
2002-03
2004-05
2006-07
2008